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Effect of the vancomycin minimum inhibitory concentration on clinical outcomes in patients with methicillin-susceptible *Staphylococcus aureus* bacteraemia: a systematic review and meta-analysis

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ABSTRACT

Objective The use of the vancomycin minimum inhibitory concentration (MIC) as a prognostic predictor in patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) has been debated in the last decade. We performed a systematic review and meta-analysis to investigate whether an elevated vancomycin MIC is associated with a worse prognosis for patients with MSSA bacteraemia.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase and the Cochrane Library were searched from inception to December 2019.

Eligibility criteria Randomised controlled trials or observational studies were considered eligible if they provided clinical outcomes of patients with MSSA bacteraemia, stratified by vancomycin MIC.

Data synthesis Primary outcome was mortality. Secondary outcomes included septic thrombophlebitis, persistent bacteraemia and complicated bacteraemia. Pooled ORs and 95% CIs were calculated. Subgroup analyses included the susceptibility testing method.

Results Fifteen observational studies were included. Bacteraemia due to MSSA isolates with high vancomycin MICs was associated with higher mortality than isolates with low MICs (OR 1.44; 95% CI 1.12 to 1.84; I^2=40.3%). Additionally, significantly greater septic thrombophlebitis (OR 3.16; 95% CI 1.11 to 9.00; I^2=58.6%) and a trend towards more persistent bacteraemia (OR 1.79; 95% CI 0.97 to 3.31; I^2=0%) were observed in patients with high vancomycin MICs than in patients with low MICs. Differences in complicated bacteraemia were not significant. Similar findings were obtained in subgroup analyses using Etest. However, significant differences in outcomes were not observed between the high and low vancomycin MICs detected using broth microdilution.

Conclusion The available data suggest an association between elevated vancomycin MICs detected using Etest and adverse clinical outcomes for patients with MSSA bacteraemia. Future studies should validate these findings and explore the potential mechanisms.

PROSPERO registration number CRD42018090547.

Strengths and limitations of this study

► This meta-analysis is the first study to comprehensively compare the clinical outcomes of patients with methicillin-susceptible *Staphylococcus aureus* bacteraemia with high and low vancomycin minimum inhibitory concentrations.
► Two authors independently performed the study selection, data extraction and quality assessment.
► Numerous sensitivity analyses were performed to examine the robustness of the findings.
► Subgroup analyses based on the susceptibility testing method were also performed.
► Due to insufficient details of empirical and definitive treatments, a subgroup analysis based on the antibiotic treatment could not be performed.

INTRODUCTION

Staphylococcus aureus is one of the most common causes of healthcare-associated infections. Although more publications have focused on methicillin-resistant *S. aureus* (MRSA), bacteraemia caused by methicillin-susceptible *S. aureus* (MSSA) remains a significant global healthcare burden due to its high morbidity and mortality rates.[1 2]

The recognition of potential risk factors is considered vital to improve the management of patients with MSSA bacteraemia. According to previous studies, β-lactams are superior to vancomycin in terms of survival for the treatment of MSSA bacteraemia.[3–5] Therefore, the current guidelines recommend switching therapy to a β-lactam antibiotic, such as cefazolin or antistaphylococcal penicillins (ASPs), after the identification of an MSSA infection.[6] Furthermore, our previous meta-analysis[7] systematically

evaluated studies focusing on the efficacy and safety of cefazolin versus ASPs in treating MSSA bacteraemia and found that cefazolin was significantly correlated with reductions in the death rate, clinical failure, hepatotoxicity and nephrotoxicity. The results favour cefazolin for the management of MSSA bacteraemia.

The choice of the antibiotic is a well-recognised risk factor for MSSA bacteraemia, but less is known about the effects of microbiological factors. A decade ago, two studies reported an association between a high vancomycin minimum inhibitory concentration (MIC) and a worse prognosis in terms of mortality and complicated bacteraemia among patients with MSSA bacteraemia, regardless of the antibiotic therapy used.[8 9] In 2014, Kalil et al[10] conducted a meta-analysis to identify a potential relationship between vancomycin MICs and mortality for patients with *S. aureus* bloodstream infections. Unfortunately, a subgroup analysis of MSSA bacteraemia was unable to be performed because insufficient publications were available at that time. Since then, a growing number of studies have focused on this interesting issue but have reported inconsistent results. Therefore, we conducted a systematic review and meta-analysis to assess the effect of the vancomycin MIC on clinical outcomes in patients with MSSA bacteraemia.

METHODS
Literature search
PubMed, Embase and the Cochrane Library were searched from inception to December 2019 by two investigators. The search terms and strategies for this meta-analysis are summarised in online supplemental table S1). References from identified publications and relevant reviews were also checked to identify additional articles. No language restriction was imposed.

Inclusion criteria and study selection
Two authors independently screened the literature, and discrepancies were resolved through discussion. Randomised controlled trials or observational studies were considered eligible if they provided clinical outcomes of patients with MSSA bacteraemia, stratified by vancomycin MIC. Broth microdilution (BMD), automated BMD (eg, Microscan), and Etest were considered reasonable susceptibility testing methods. The following types of studies were excluded: (1) the study population did not consist of patients with MSSA bacteraemia, (2) solely paediatric studies, (3) no outcome data were available, (4) duplicate publications and (5) conference abstracts.

Data extraction and quality assessment
Two reviewers independently extracted the data, and discrepancies were resolved by consensus. The following information was collected: study design, countries where the study was conducted, study period, sample size, patient characteristics (age, sex, comorbidity, severity of illness,

and proportions of endocarditis), vancomycin MIC testing method, cut-off value, antimicrobial therapy used and the clinical outcomes. The Risk of Bias in Nonrandomized Studies for Interventions (ROBINS-I) tool was used to assess the quality of observational studies.[11]

Definitions and outcomes
The primary outcome was mortality. When data from more than one time point were available, the mortality at the latest point reporting the largest number of deaths was used in the main analysis (eg, 30-day mortality had precedence over 14-day mortality). The secondary outcomes included septic thrombophlebitis, persistent bacteraemia, and complicated bacteraemia, as defined by the individual. If vancomycin MIC was detected using multiple methods, the data from the reference BMD method were adopted in the main analysis. We did not define specific cut-off points for the vancomycin MIC because different criteria were used in various studies.

Statistical analysis
The ORs and 95% CIs for outcomes were calculated. If adjusted ORs were provided in the included studies, then they were used for data combination. Otherwise, unadjusted ORs were used for data combination. Heterogeneity was assessed using the I^2 statistic, and a value of >50% was considered significant heterogeneity.[12] The fixed effects model was used when significant heterogeneity was not present; otherwise, the random effects model was used. For the outcomes using fixed effects model, we also calculated the random effects model for additional analyses to provide conservative pooling estimates. Subgroup analyses were performed based on the susceptibility testing method (Etest and BMD). Sensitivity analyses were conducted for the primary outcome by removing each study individually. Additional sensitivity analyses were performed by restricting studies that were classified according to a specific criterion, such as prospective, large-sample (n≥90), high-quality (low to moderate risk of bias in 'overall assessment' of ROBIN-I tool), unadjusted mortality rate, adjusted mortality rate and 30-day mortality rate (the most frequent mortality rate reported). Publication bias was estimated by constructing a funnel plot and Egger's test. All the statistical analyses in the present meta-analysis were performed using STATA software V.15.0 (StataCorp, serial NO. 301506351850). The significance threshold was set to 0.05.

RESULTS
Search results
Fifteen studies[8 9 13–25] involving 2487 participants met the inclusion criteria. The details regarding identification of relevant studies are shown in figure 1. Two studies[17 26] contained duplicate patients and the study with smaller sample size[26] was excluded.

All studies were published within the last decade, and the number of patients per study ranged from 53 to 334.
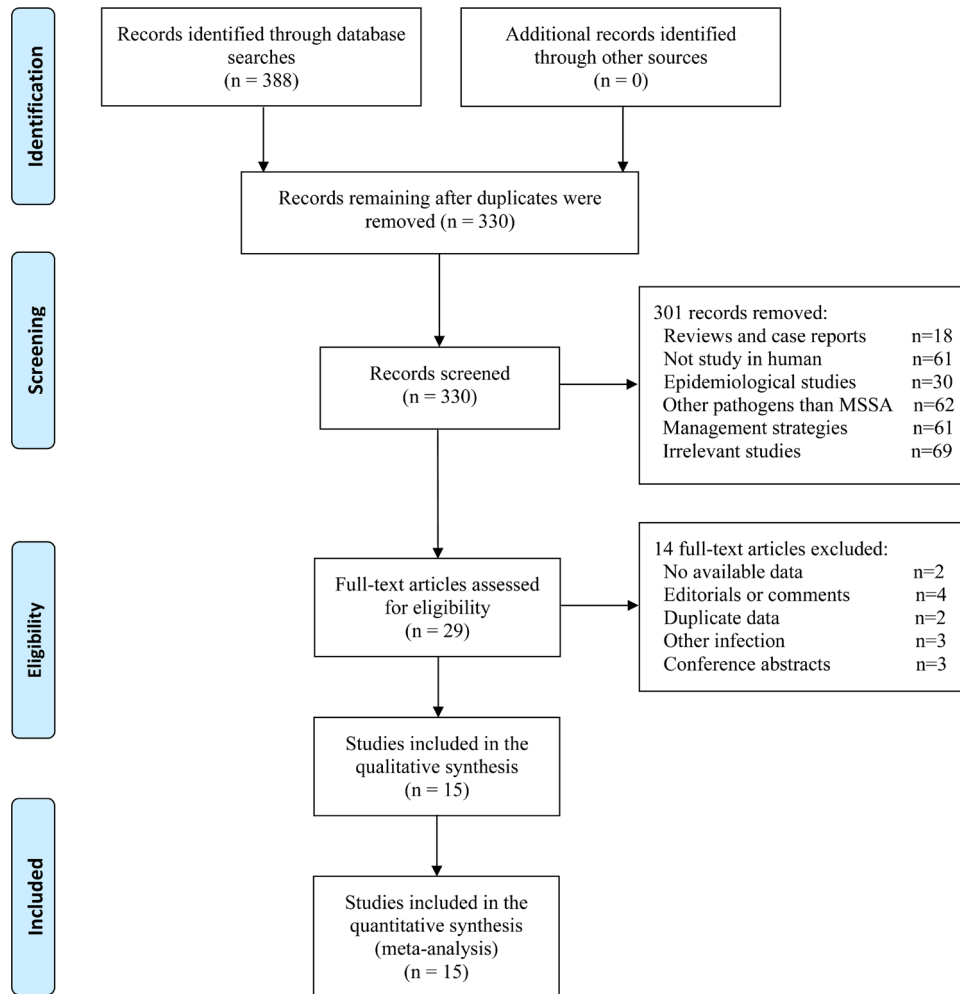
Figure 1 Flow diagram of the literature search and selection process. MSSA, methicillin-susceptible *Staphylococcus aureus*.

Eight studies were prospective observational studies, and the others were retrospective studies. The proportion of females ranged from 28% to 54.7%, and the mean or median age ranged from 60 to 68 years. Most studies were conducted in Europe (n=10), followed by the USA (n=3) and South Korea (n=1); the remaining study was conducted in multiple countries (Australia and New Zealand). Most of the studies used the Etest method to determine the vancomycin MIC and chose an MIC value ≥1.5 µg/mL as the cut-off for a high vancomycin MIC. Additional details of the characteristics are presented in table 1. Raw data for outcomes extracted from the included studies are presented in online supplemental table S2-S5). Risk-of-bias assessment showed that six studies[13 15 18 22–24] had an overall critical risk of bias, and nine studies[8 9 14 16 17 19–21 25] had an overall low to moderate risk of bias (online supplemental table S6).

Primary outcome: mortality

Fourteen studies reported mortality rates.[8 9 13–17 19–25] The mortality rates of MSSA bacteraemia varied among studies from 12% to 43% (table 1). Overall, the main analysis using a fixed effects model showed the mortality rate for patients infected with MSSA isolates with a high

vancomycin MIC was significantly higher than isolates with a low MIC (OR 1.44; 95% CI 1.12 to 1.84; I^2=40.3%; figure 2). The additional analysis using the random effects model showed similar results (OR 1.52; 95% CI 1.08 to 2.12; I^2=40.3%; table 2). Sensitivity analyses limited to 14 studies providing unadjusted mortality rates (OR 1.42; 95% CI 1.13 to 1.79; I^2=36.0%), 6 studies providing adjusted mortality rates (OR 1.74; 95% CI 1.16 to 2.60; I^2=47.9%) and 12 studies reporting 30-day mortality rates (OR 1.44; 95% CI 1.09 to 1.92; I^2=28.2%; table 3) did not substantially alter the results of the main analysis. Similar results were obtained using the leave-one-out method (online supplemental table S7) and other prespecified sensitivity analyses (table 3).

Secondary outcomes

Secondary outcome data were available in nine studies,[8 13 15–18 21 22 24] and the definitions are shown in online supplemental table S8. Six studies reported septic thrombophlebitis.[8 15–17 21 22] An increased risk of septic thrombophlebitis was observed in patients with a high vancomycin MIC compared with patients with a low MIC in the pooled analysis using the random effects model (OR 3.16; 95% CI 1.11 to 9.00; I^2=58.6%; figure 3). Four

Table 1 Characteristics of the studies included in the meta-analysis

| Study	Study design	Location	Study period	Sample size	Female %	Age, year	Assay method (HVM cut-off, mg/L)	Comorbidity and disease severity scores *	IE % *	Empirical treatment *	Definitive treatment *	Mortality %	Mortality definition
Abelenda Alonso et al[13]	Ret	Spain	2014–2016	58	41.4	68	BMD (≥2.0)	NR	5.2	Consistent with guidelines 29.31%, VAN 24.13%, DAP 1.72%	VAN 22.41%, DAP 5.17 %, LIN 6.89%, CLO 39.65%	25.9	30 days
Aguado et al[8]	Ret	Spain	2002–2004	99	33.3	63	Etest (≥1.5)	Mean CCI 3.4 versus 2.8	7.1	GLY 78.3% versus 60.5%; ASBL 21.7% versus 26.3%	NR	14.1	30 days
Baxi et al[14]	Pro	USA	2008–2013	230	NR	NR	MicroScan (≥2.0)	NR	NR	NR	NR	16.1 and 11.7	90 days, 30 days
Bouiller et al[15]	Pro	France	2009–2011	250	40.8	68	Etest (≥1.5)	NR	8.8	ASBL 57.8% versus 58.6% versus VAN 9.4% versus 16.1%	Appropriate first line 96.9% versus optimal first line 15.6% versus 11.8%	25.6	30 days
Caston et al[16]	Ret	Spain	NR	53	54.7	68	MicroScan (≥2.0)	Mean CCI 3.0 versus 2.9	5.7	ASBL 54.5% versus 40.6%; GLY 4.5% versus 19.4%; others 38.1% versus 34.3%	NR	22.6	30 days
Cervera et al[17]	Pro	Spain	1995–2011	93	28.0	60	Etest (≥1.5)	Median CCI 2 versus 1	100	NR	CLO 100% versus 100%	43.0 and 39.8	One-year and in-hospital
Falcón et al[18]	Ret	Spain	2013–2018	113	NR	NR	BMD (≥0.75 or 0.5), Etest (≥1.5)	NR	NR	NR	NR	NR	NR
Fernandez-Hidalgo et al[19]	Pro	Spain	2013–2016	173	39.1	65	Etest (≥1.5)	NR	100	ASBL 100% versus 100%	NR	33.5	In-hospital
Han et al[20]	Ret	USA	2007–2009	202	NR	NR	Etest (> 1.0)	NR	NR	VAN 60.9%	β-lactams 79.2%	12.4	30 days
Holmes et al[9]	Pro	Australia and New Zealand	2007–2008	330	32.4	60	Etest (> 1.5), BMD (NR)	NR	10.0	NR	FLU 80.6%, VAN 19.4%	13.9	30 days
López-Cortés et al[21]	Pro	Spain	2008–2011	135	41.5	67	Etest (≥1.5)	Median CCI 1 versus 2, median PBS 1 versus 2	8.1	NR	CLO 76.9% versus 85.7%, GLY 0 versus 8.2%, ASBL other than CLO 15.4% versus 5.1%	27.4 and 20.7	30 days and 14 days

Continued

Table 1 Continued

Study	Study design	Location	Study period	Sample size	Female %	Age, year	Assay method (HVM cut-off, mg/L)	Comorbidity and disease severity scores *	IE % *	Empirical treatment *	Definitive treatment *	Mortality %	Mortality definition
San-Juan et al[22]	Pro	Spain	2011–2014	83	41.0	60	Etest (≥1.5)	Mean CCI 4.0 versus 3.5, mean PBS 1.1 versus 1.5	2.4	ASBL 51.1% versus 52.5%, GLY 37.2% versus 40%, DAP 23.2% versus 17.5%	ASBL 100% versus 96.25%	12.0	30 days
Song et al[23]	Pro	South Korea	2009–2011	334	NR	NR	BMD (≥2.0), Etest (≥1.5)	NR	7.2	NR	Cephalosporin 48.1% versus 43.8%, NAF 29.6% versus 24.9%, GLY 22.2% versus 31.3%	24.9	30 days
Sullivan et al[24]	Ret	USA	2010–2012	252	41.3	60	MicroScan (≥2.0), Etest (NR)	Mean CCI 5.1 versus 5.5, mean PBS 2.4 versus 2.2	NR	VAN 77% versus 62%; ASBL 17% versus 33%	NR	26.2, 23.4 and 17.8	90 days, 60 days, and 30 days
Viedma et al[25]	Ret	Spain	2010–2011	84	39.3	62	Etest (≥1.5)	NR	NR	NR	β-lactams 58.2% versus 65.5%, VAN 3.6% versus 24.1%	38.1 and 20.2	In-hospital and 30 days

*High vancomycin MIC versus low vancomycin MIC.

ASBL, anti-staphylococcal β-lactams; BMD, broth microdilution; CCI, Charlson Comorbidity Index; CLO, cloxacillin; DAP, daptomycin; FLU, flucloxacillin; GLY, glycopeptides; HVM, high vancomycin minimum inhibitory concentration; IE, infective endocarditis; LIN, linezolid; LVM, low vancomycin minimum inhibitory concentration; MIC, minimum inhibitory concentration; NAF, nafcillin; NR, not reported; PBS, Pitt bacteraemia score; Pro, prospective; Ret, retrospective; VAN, vancomycin.
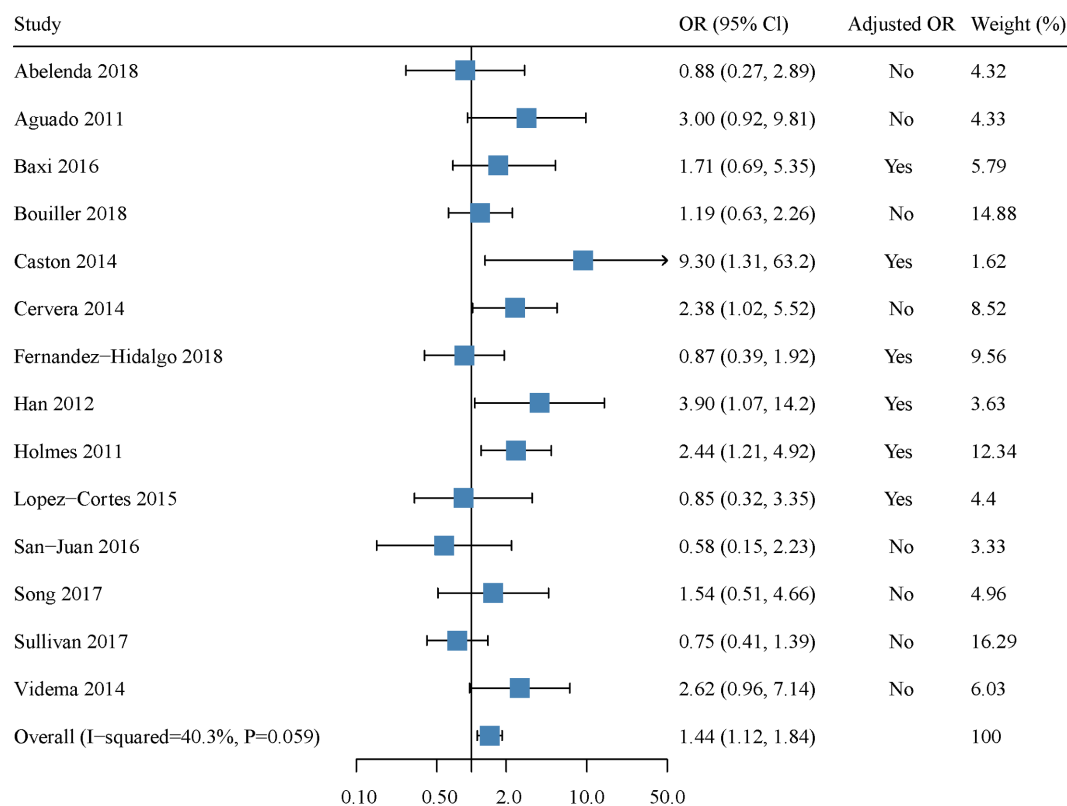
Figure 2 Forest plot of ORs for mortality.

studies reported persistent bacteraemia.[13 17 21 22] The meta-analysis using the fixed effects model revealed a non-significant higher risk of persistent bacteraemia in patients with a high vancomycin MIC (OR 1.79; 95% CI 0.97 to 3.31; I^2=0%; figure 4). The additional analysis using the random effects model supported the main conclusions (table 2). Seven studies reported complicated bacteraemia,[8 15 16 18 21 22 24] and no significant difference

was observed in the pooled analysis using the random effects model (OR 1.59; 95% CI 0.58 to 4.37; I^2=87.0%; figure 5).

Subgroup analysis and publication bias

In the subset of studies using Etest, patients with a high vancomycin MIC still exhibited a significantly higher mortality rate (OR 1.62; 95% CI 1.21 to 2.17; I^2=27.6%)

Table 2 Subgroup analyses of outcomes

Outcomes	Susceptibility testing method	No. of studies	I^2 %	Estimates from fixed effect models		Estimates from random effect models	
				OR (95% CI)	P value	OR (95% CI)	P value
Mortality	Etest	10	27.6	1.62 (1.21 to 2.17)	0.001	1.63 (1.15 to 2.32)	0.006
	BMD	5	45.7	1.12 (0.73 to 1.71)	0.617	1.32 (0.69 to 2.52)	0.394
	Overall	14	40.3	1.44 (1.12 to 1.84)	0.004	1.52 (1.08 to 2.12)	0.015
Septic thrombophlebitis	Etest	5	57.3	Not performed	Not applicable	4.06 (1.40 to 11.8)	0.031
	BMD	1	Not available	Not performed	Not applicable	Not performed	Not applicable
	Overall	6	58.6	Not performed	Not applicable	3.16 (1.11 to 9.00)	0.031
Persistent bacteraemia	Etest	3	0	1.56 (0.76 to 3.21)	0.224	1.56 (0.76 to 3.21)	0.224
	BMD	1	Not available	Not performed	Not applicable	Not performed	Not applicable
	Overall	4	0	1.79 (0.97 to 3.31)	0.064	1.79 (0.97 to 3.31)	0.064
Complicated bacteraemia	Etest	5	90.1	Not performed	Not applicable	1.92 (0.45–8.25)	0.378
	BMD	3	59.0	Not performed	Not applicable	1.43 (0.58–3.51)	0.438
	Overall	7	87.0	Not performed	Not applicable	1.59 (0.58–4.37)	0.365

BMD, broth microdilution.

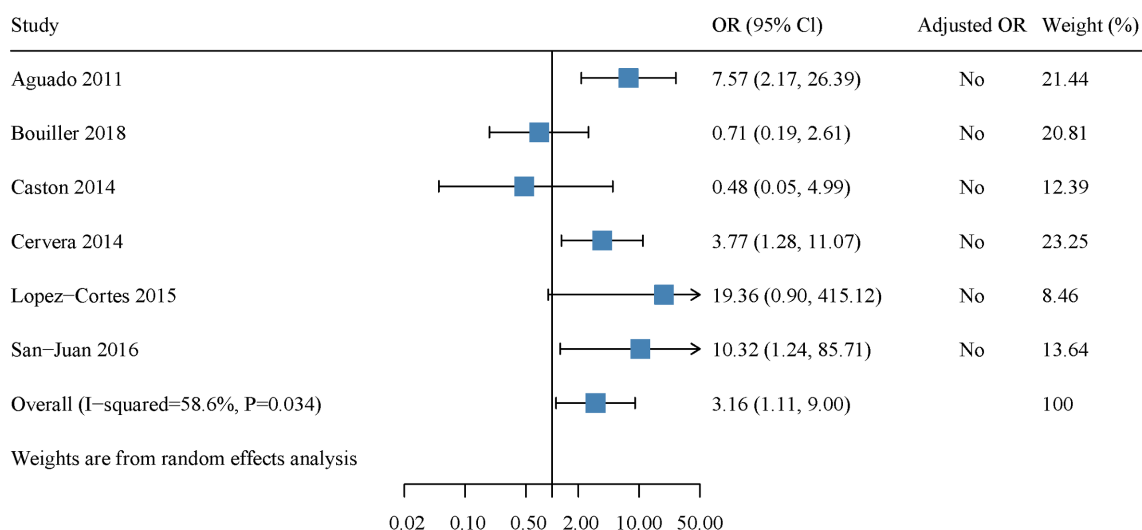**Table 3** Sensitivity analyses of mortality

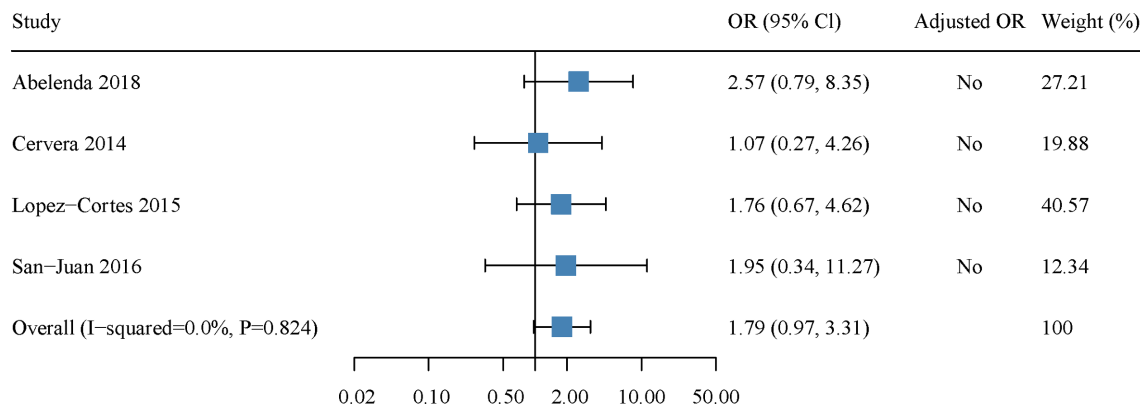| Term included	No. of studies included	OR (95% CI)	P value	I2 %
Prospective	8	1.42 (1.04 to 1.93)	0.026	13.0
Large sample (n≥90)	10	1.48 (1.04 to 2.11)	0.012	37.6
Low-to-moderate overall risk of bias	9	1.99 (1.43 to 2.76)	<0.001	27.0
Adjusted mortality	6	1.74 (1.16 to 2.60)	0.007	47.9
Unadjusted mortality	14	1.42 (1.13 to 1.79)	0.003	36.0
30-day mortality	12	1.44 (1.09 to 1.92)	0.011	28.2

and septic thrombophlebitis (OR 4.06; 95% CI 1.40 to 11.80; I^2=57.3%) than patients with a low MIC. However, no significant differences in outcomes were observed between the high and low vancomycin MIC values detected using BMD (table 2). The results of the additional analyses using the random effects model supported the main conclusions (table 2). A visual inspection of the funnel plot showed symmetry (online supplemental figure S1), and the Egger test did not indicate significant publication bias (p=0.546).

DISCUSSION

To our knowledge, this systematic review and meta-analysis are the first to comprehensively compare the clinical outcomes of patients with MSSA bacteraemia presenting high and low vancomycin MICs. The main findings of the present study indicate that an elevated vancomycin MIC correlates with a higher mortality rate. The findings were relatively robust and were not significantly changed during the sensitivity analyses. In addition, patients with a high vancomycin MIC had a significantly higher risk of septic thrombophlebitis and a trend towards more persistent bacteraemia. No significant difference was observed in complicated bacteraemia. Based on these findings, the vancomycin MIC is potentially useful to predict adverse outcomes in patients with MSSA bacteraemia.

Several meta-analyses exploring the effect of the vancomycin MIC on the mortality rate in patients with a MRSA infection have produced positive correlations; the failure to achieve the pharmacokinetic/pharmacodynamic targets of vancomycin may be the main explanation.[27–29] However, vancomycin is not routinely used in clinical practice after the identification of an MSSA infection. In fact, the proportion of patients who received vancomycin for definitive therapy is less than one quarter in the included studies (table 1). By analysing the subset of patients with MSSA bacteraemia treated with flucloxacillin, Holmes et al observed a significant correlation between the 30-day mortality rate and a high vancomycin MIC.[9] Similar results were reported in the included study by Cervera et al, which included patients who exclusively received cloxacillin.[17] We hypothesise that a decreased vancomycin susceptibility might be a surrogate marker of a weak response to both vancomycin and other antibiotics (eg, β-lactams) in the treatment of MSSA infections. Interestingly, MSSA isolates with decreased susceptibility to vancomycin also exhibit less susceptibility to the ASP and daptomycin.[30] This phenomenon might have contributed to special structural modifications in the cell walls of isolates with an elevated vancomycin MIC, particularly an increased cell wall thickness.[31] Moreover, reductions in autolysin activity and in the cell wall content of

Study		OR (95% CI)	Adjusted OR	Weight (%)
Aguado 2011		7.57 (2.17, 26.39)	No	21.44
Bouiller 2018		0.71 (0.19, 2.61)	No	20.81
Caston 2014		0.48 (0.05, 4.99)	No	12.39
Cervera 2014		3.77 (1.28, 11.07)	No	23.25
Lopez−Cortes 2015		19.36 (0.90, 415.12)	No	8.46
San−Juan 2016		10.32 (1.24, 85.71)	No	13.64
Overall (I−squared=58.6%, P=0.034)		3.16 (1.11, 9.00)		100

Weights are from random effects analysis

0.02 0.10 0.50 2.00 10.00 50.00

Figure 3 Forest plot of ORs for septic thrombophlebitis.

Study		OR (95% CI)	Adjusted OR	Weight (%)
Abelenda 2018		2.57 (0.79, 8.35)	No	27.21
Cervera 2014		1.07 (0.27, 4.26)	No	19.88
Lopez−Cortes 2015		1.76 (0.67, 4.62)	No	40.57
San−Juan 2016		1.95 (0.34, 11.27)	No	12.34
Overall (I−squared=0.0%, P=0.824)		1.79 (0.97, 3.31)		100

Figure 4 Forest plot of ORs for persistent bacteraemia.

penicillin binding protein 4 may be involved in these changes.[32]

The elevated vancomycin MIC might also be a marker for unfavourable bacterial or genetic factors that lead to adverse outcomes in patients with MSSA bacteraemia. The accessory gene regulator (*agr*) is a quorum-sensing regulator that is responsible for the expression of various virulence factors.[33] *Agr* dysfunction and *agr* type II have been correlated with an elevated vancomycin MIC, increased mortality rate, more persistent bacteraemia and increased biofilm formation.[25 34–37] Moreover, we noticed that *agr* type III was less prevalent in MSSA isolates with a high vancomycin MIC than in isolates with a low MIC (17.2% vs 34.0%) in the study by Lopez-Cortes *et al*,[21] although this difference did not reach statistical significance. In fact, the negative correlation between *agr* type III and mortality was observed in MSSA infective endocarditis.[19]

Multiple clonal complexes (CCs), including CC5, CC8, CC88 and CC188, are associated with reduced vancomycin susceptibility in *S. aureus* bacteraemia isolates.[25 34] A recent study[38] analysed the genotypic profiles among 93 MSSA isolates reported in the study by Cervera *et al*[17] and

found that CC5 was significantly correlated with a higher mortality rate in the univariate analysis. Another included study[19] also revealed a correlation between MSSA isolates harbouring CC8 and increased in-hospital mortality in the univariate analysis.

Furthermore, specific resistance and virulence genes (including *blaZ, sea, clfA,* and *splA*) and the arginine catabolic mobile element locus were linked with an elevated vancomycin MIC in *S. aureus* bacteraemia.[34] MSSA isolates with genotypes *spa*-002 and *spa*-CC008 correlate with an elevated vancomycin MIC,[24] and isolates with extracellular fibrinogen binding protein and serine endopeptidase are associated with a higher incidence of embolism.[26]

Overall, the mechanism underlying the association between the increased vancomycin MIC and adverse outcomes in patients with MSSA bacteraemia appear to be complex. We postulate that this correlation is not attributed to a single cause, but results from the interactive effects of multiple factors. The findings of the present meta-analysis highlight the need for further studies to fill the knowledge gap about this interesting issue.

Study		OR (95% CI)	Adjusted OR	Weight (%)
Aguado 2011		22.9 (6.70, 78.1)	Yes	13.58
Bouiller 2018		0.29 (0.14, 0.60)	No	15.62
Caston 2014		0.32 (0.06, 1.66)	No	11.64
Falcon 2019		1.72 (0.66, 4.48)	No	14.75
Lopez−Cortes 2015		0.97 (0.30, 3.19)	No	13.79
San−Juan 2016		2.88 (1.08, 7.70)	No	14.65
Sullivan 2017		2.35 (1.26, 4.37)	Yes	15.97
Overall (I−squared=87.0%, P=0.000)		1.59 (0.58, 4.37)		100

Weights are from random effects analysis
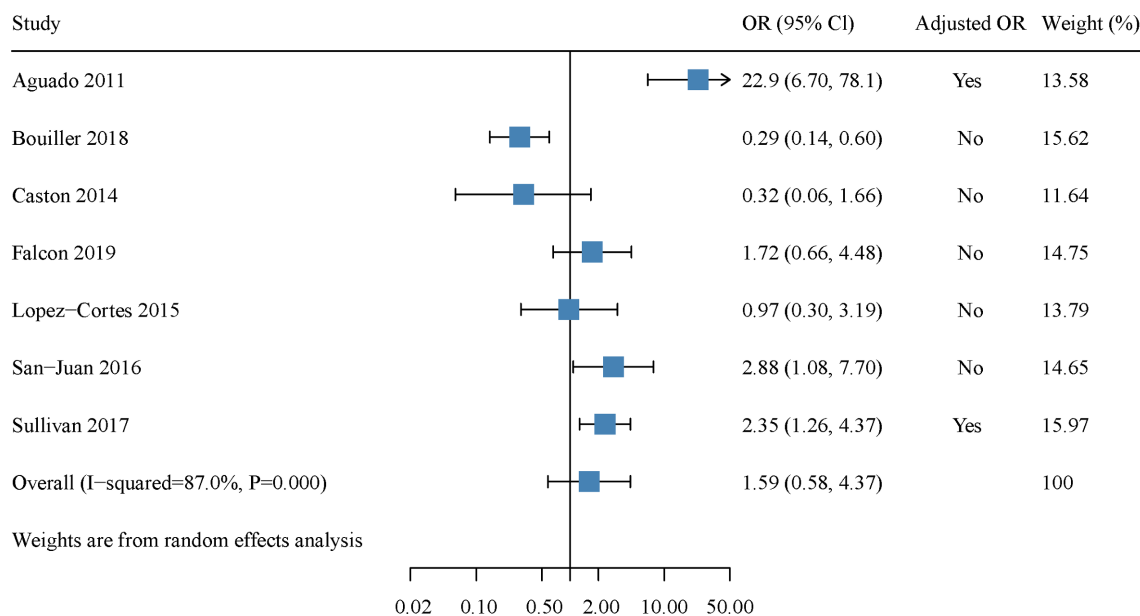
Figure 5 Forest plot of ORs for complicated bacteraemia.

Notably, the most frequently used test to detect the vancomycin MIC in the included studies was the Etest. We identified a few studies performed susceptibility testing using Etest in parallel with manual or automated BMD methods. According to Han *et al*, the vancomycin MIC detected using Etest poorly correlated with the values obtained using the BMD method.[20] Song *et al* reported the consistent underestimation of the MIC values from Etest among isolates with a high vancomycin MIC (2 mg/L) and overestimated among isolates with a low MIC (0.5 mg/L) using BMD.[23] As shown in the study by Sullivan *et al*, the vancomycin MIC values measured using automated BMD (Microscan) are consistently higher than the values measured using Etest in the majority of MSSA isolates.[24] Because the application of the various susceptibility testing methods may introduce bias, we conducted a subgroup analysis according to the MIC methodology. In the subgroup analysis of studies using Etest, patients with a high vancomycin MIC still had a significantly higher mortality rate than patients with a low MIC. However, no significant difference was observed in the subgroup analysis of studies using BMD. Notably, we did not include the study by Holmes *et al*[9] in the subgroup analysis of studies using BMD due to the unavailability of data, although the authors stated that a higher mortality rate was correlated with an increased vancomycin MIC detected using BMD. Therefore, the results of the subgroup analysis of studies using BMD may be underestimated. Nevertheless, the present meta-analysis indicated that Etest might be better for predicting clinical outcomes, although the reproducibility and interobserver variation may be a concern, as noted by Falcón *et al*.[39] Because the BMD is still the reference method for vancomycin susceptibility testing, more studies using the BMD are needed to validate the association between vancomycin MIC and clinical outcomes.

The present meta-analysis has several limitations that should be considered when interpreting the results. First, all studies included in the meta-analysis were observational studies containing many confounding factors. However, only six out of the included studies were designed to adjust for confounding factors and reported adjusted mortality rates. For studies without adjustment for potential confounders, the baseline characteristics of the patients (eg, underlying conditions and the calculation of severity scores) between the high and low vancomycin MIC groups may influence the outcomes. For example, patients with high vancomycin MICs had numerically higher mean or median CCI scores in several studies.[17 22] Bouiller *et al* observed more dialysis and a higher proportion of ultimately fatal disease in the high vancomycin MIC group.[15] More underlying diseases and higher CCI scores might be associated with adverse outcomes. Therefore, the adverse effect of the high vancomycin MIC on clinical outcomes might be overestimated. Second, almost half of the studies were retrospective in design, which may introduce inherent selection bias into this report. To address the potential confounding bias and selection bias, numerous sensitivity analyses were performed. Sensitivity analyses limited to prospective studies, high-quality studies based on the

ROBIN-I tool, and studies providing adjusted mortality data did not substantially alter the results of the main analysis, further supporting the conclusions in our study. Third, as we mentioned in the Introduction section, the choice of antibiotic is closely related to the survival of patients with MSSA bacteraemia. However, the dose and duration of antibiotic therapy and the types of β-lactams chosen were not reported in most included studies. Due to insufficient details regarding both empirical and definitive treatments, a subgroup analysis based on the antibiotic treatment was unable to be conducted. Moreover, our previous findings regarding the differences in efficacy and safety between cefazolin and ASPs have not been sufficiently considered in the included studies.[7] Fourth, most MSSA isolates in the included studies had a vancomycin MIC ≤2 mg/L determined using BMD or ≤1.5 mg/L determined using Etest, and the outcomes of MSSA bacteraemia caused by more resistant isolates are unclear.

In conclusion, the available data suggest a correlation between a high vancomycin MIC detected using Etest and adverse clinical outcomes for patients with MSSA bacteraemia. More well-designed studies are warranted to validate the present findings and to explore the potential mechanisms.

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